Antihyperuricemics

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS[1,2]

Drug	Manufacturer	Indication(s)
allopurinol (Zyloprim®)[3]	generic	▪ Management of patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy). ▪ Management of patients with leukemia, lymphoma and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels. ▪ Management of patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients.
colchicine (Colcrys™)[4]	AR Scientific	▪ Gout flares – treatment and prevention ▪ Management of Familial Mediterranean Fever in adults and children ages four years and older
febuxostat (Uloric®)[5]	Takeda	▪ Chronic management of hyperuricemia in patients with gout
pegloticase (Krystexxa®)[6]		▪ Treatment of chronic gout in adult patients refractory to conventional therapy
probenecid	generic	▪ Prophylaxis of hyperuricemia ▪ Treatment of hyperuricemia associated with chronic gout or secondary to other causes ▪ Adjunctive therapy for Treatment of Gonorrhea with penicillin or ampicillin ▪ Adjunctive therapy for antibiotic treatment
probenecid – colchicine	generic	▪ Treatment of chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout

Allopurinol, febuxostat, and pegloticase are not recommended for the treatment of asymptomatic hyperuricemia.

Multisource colchicine has not demonstrated bioequivalence to an innovator product; therefore, multisource colchicine products are not considered generics nor have the multisource products received Food and Drug Administration (FDA) approval. On September 30, 2010, the FDA halted marketing of unapproved colchicine products. Interstate shipping of unapproved colchicine ceased the end of December 2010.[7]

OVERVIEW

Hyperuricemia (serum uric acid > 6.8 mg/dL) can occur due to either an overproduction of uric acid or an under excretion of uric acid or a combination of the two mechanisms.[8] Most often, hyperuricemia results are due to a reduction in fractional clearance of urate rather than an over production of urate. Urate under excretion can occur as a result of both primary and secondary hyperuricemia. Secondary hyperuricemia may be due to renal impairment; hypertension; drugs including low dose aspirin, diuretics, ethanol, and cyclosporine; lead nephropathy; and hypothyroidism.[9,10] Urate over production may occur due to primary hyperuricemia, Lesch-Nyhan syndrome (an inborn error in metabolism) and due to salvaged purines from rapid cell turnover or inflammatory disorders including lympho-myeloproliferative disorders and severe exfoliative psoriasis, and cytotoxic drugs. Hyperuricemia is the most important risk factor for developing gout.

Gout is the crystal deposition of monosodium urate associated with elevated levels of uric acid. Crystals are deposited in joints, tendons and surrounding tissues. Acute attacks of gout are painful and in over approximately half of all cases, the metatarsophalangeal joint of the great toe was the first joint to be affected. Over time, deposition of masses of urates in joints creates tophi.

Treatment of gout is managed in three stages: acute treatment, prophylaxis to prevent acute flares, and lowering excess stores of urate to prevent flares of gouty arthritis and prevent tissue deposition of urate crystals. Acute gouty arthritis can be treated with colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), and intra-articular corticosteroid injections.

After an initial gout attack, the choice of urate-lowering medications is uricosuric drugs or xanthine oxidase inhibitors. Probenecid promotes uric acid excretion by inhibiting the tubular reabsorption of filtered and secreted urate, thereby increasing urate excretion. Some patients with gout can experience an increased incidence of uric acid stones due to increased uric acid renal clearance. This condition could lead to renal calculi or colic, hematuria, or costovertebral pain. Urine should be kept alkaline to increase the solubility of uric acid and decrease the risk of developing nephrolithiasis. Probenecid can increase the number of acute gouty attacks occurring in the first six to 12 months of therapy.

The xanthine oxidase inhibitors, allopurinol and febuxostat, inhibit uric acid production. With allopurinol, serum urate concentrations begin to decrease within one to two days, although significant reductions may not be immediately evident due to the dissolution of uric acid deposits. Normal serum urate concentrations are usually achieved within one to three weeks. If allopurinol is discontinued, uric acid concentrations may return to pretreatment levels, which usually occurs seven to ten days after allopurinol discontinuation. No studies with febuxostat have been conducted in patients with secondary hyperuricemia (including patients being treated for Lesch-Nyhan syndrome or malignant disease, or in organ transplant recipients); therefore, febuxostat is not recommended for use in these patients. Febuxostat offers an alternative to allopurinol for patients who fail to achieve serum urate less than 6 mg/dL after three months of therapy or who are intolerant of allopurinol.

Colchicine (Colcrys) is FDA-approved as an orphan drug for the treatment of Familial Mediterranean Fever (FMF). FMF is an autosomal recessive disorder characterized by recurrent episodes of painful inflammation in the abdomen, chest, or joints. These episodes are often accompanied by fever and sometimes a rash. The first episode usually occurs in childhood or adolescence, but in some cases, the initial attack occurs much later in life. Typically, episodes last 12 to 72 hours and can vary in severity. The length of time between attacks is also variable. Without treatment to help prevent attacks and complications, a buildup of amyloid in the body's organs and tissues may occur, which can lead to kidney failure. FMF primarily affects populations originating in the Mediterranean region, particularly people of Armenian, Arabic, Turkish, and Jewish ancestry. The disorder affects from 1 in 250 people to 1 in 1,000 people in these populations.

Mutations in the MEFV gene cause FMF. The MEFV gene provides instructions for making a protein called pyrin, which is found in white blood cells. Pyrin is involved in the immune system, helping to regulate the process of inflammation. When inflammation and resolution of the offending stimulus has been accomplished, the body stops the inflammatory response to prevent damage to its own cells and tissues. Mutations in the MEFV gene reduce the activity of the pyrin protein, which disrupts control of the inflammation process. An inappropriate or prolonged inflammatory response can result, usually accompanied by fever and pain in the abdomen, chest, or joints.

In most patients dose titration of oral urate-lowering agents can adequately achieve target uric acid levels. However, it has been noted that approximately three percent of patients do not respond to oral urate-lowering medications because of refractoriness, contraindications, or intolerance. Pegloticase (Krystexxa) provides an effective alternative therapy to conventional oral urate-lowering medications for those patients who cannot take oral urate-lowering medications.[11]

In 2006, evidence based recommendations for the treatment of gout were developed that addressed the symptomatic control of acute gout, urate lowering therapy, and prophylaxis of acute attacks.[12] Recommended drugs for acute attacks were oral nonsteroidal anti-inflammatory drugs (NSAIDs), oral colchicine, or joint aspiration and injection of corticosteroid. Urate lowering therapy is indicated in patients with recurrent acute attacks, arthropathy, tophi, or radiographic changes of gout. Allopurinol is effective long term urate lowering therapy. If allopurinol toxicity occurs, options include xanthine oxidase inhibitors, allopurinol desensitization, or a uricosuric agent. Febuxostat was not available at the time of guideline development, but in a 2008 review, febuxostat was noted only to be used in those patients intolerant of allopurinol. Nothing else changed in the guidelines. When gout is associated with the use of diuretics, the diuretic should be discontinued if possible. For prophylaxis against acute attacks, either colchicine 0.5-1 mg daily or an NSAID, with gastroprotection if indicated, are recommended. Pegloticase (Krystexxa) was not available at the time the guidelines were developed or reviewed.

In 2007, the British Society for Rheumatology and British Health Professionals in Rheumatology established guidelines for the management of gout.[13] In an acute attack, maximal doses of NSAIDs should begin immediately and continue for one to two weeks unless contraindicated. Prescribers should consider the value of gastroprotective agents (proton pump inhibitors) in patients with increased risk of peptic ulcers, bleeds or perforations. Colchicine is effective, but it works more slowly than NSAIDs. In order to reduce the risk of adverse effects, especially diarrhea, colchicine is used at a dose of 0.5-0.6 mg once to twice daily. Xanthine oxidase inhibitor therapy should not be initiated during an acute attack, but four to six weeks after the acute episode; however, in patients already on allopurinol or febuxostat therapy should not be stopped. Opiate analgesics may be used as adjuncts for pain. Corticosteroids, given orally, intramuscularly, intravenously, or intra-articularly, are an effective treatment in the management of acute gout in patients who cannot tolerate NSAIDs or are refractory to other treatments. Intra-articular corticosteroids are highly effective for acute gouty arthritis in one joint. If diuretics are being used for management of hypertension, an alternative treatment should be considered, except in patients with heart failure. Pegloticase (Krystexxa) was not available at the time these guidelines were established.

Rasburicase (Elitek®), a recombinant injectable urate oxidase, is approved for use in preventing complications of hyperuricemia during the tumor lysis syndrome, but it is not included in this review.

PHARMACOLOGY[14,15]

Drug Mechanism of Action	Mechanism of Action
allopurinol	▪ Xanthine oxidase inhibitor blocks the conversion of hypoxanthine to xanthine and of xanthine to uric acid. ▪ Unlike uricosuric agents which increase the urinary excretion of uric acid, allopurinol interferes with the catabolism of purines. Concentrations of uric acid in the blood and urine are thereby lowered. Oxypurinol, an allopurinol metabolite, also inhibits xanthine oxidase and is the agent responsible for the pharmacologic effects of allopurinol. Although hypoxanthine and xanthine serum concentrations increase, their renal clearance is at least 10 times that of uric acid.
colchicine (Colcrys)[16]	▪ Colchicine binds to proteins in microtubules of neutrophils and inhibits the migration of neutrophils into the area of inflammation, thereby interfering with the inflammatory response to urate crystal deposition. Although colchicine does not inhibit phagocytosis of uric acid crystals, it does appear to prevent the release of an inflammatory glycoprotein from phagocytes. ▪ Colchicine arrests metaphase due to two separate antimitotic effects: disruption of mitotic spindle formation and disruption of sol-gel formation. These actions also may contribute to its antigout properties. Toxic effects of colchicine are related to its antimitotic activity within proliferating tissues such as the skin, hair, and bone marrow. ▪ The mechanism of action of colchicine in patients with FMF has not been fully elucidated; however, evidence suggests that colchicine may interfere with the intracellular processes present in neutrophils and monocytes that mediate activation of interleukin-1 beta. ▪ Colchicine inhibits β-tubulin polymerization into microtubules which disrupts cytoskeletal functions and prevents neutrophil activation, degranulation, and migration which is thought to mediate some symptoms of gout.
febuxostat (Uloric)[17]	▪ Xanthine oxidase inhibitor that achieves its therapeutic effect by decreasing serum uric acid. Febuxostat is not anticipated to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations.
pegloticase (Krystexxa)[18]	▪ Pegloticase is a uric acid specific enzyme which is PEGylated and acts by catalyzing the oxidation of uric acid to allantoin which lowers serum uric acid.
probenecid	▪ Probenecid competitively inhibits the active reabsorption of urate at the proximal renal tubule; it increases the urinary excretion of uric acid and lowers serum urate concentrations. By lowering serum concentrations of uric acid below its solubility limits, probenecid may decrease or prevent urate deposition, tophi formation, and chronic joint changes; promote resolution of existing urate deposits; and, after several months of therapy, reduce the frequency of acute attacks of gout. ▪ Antibiotic therapy adjunct—Probenecid is a competitive inhibitor of the secretion of weak organic acids, including penicillins and some of the cephalosporin antibiotics, at the proximal and distal renal tubules. It thereby increases blood concentrations of these antibiotics (penicillin concentrations may increase 2- to 4-fold), increases their elimination half-life, and prolongs their duration of action.
probenecid – colchicine	▪ Colchicine relieves the pain of acute attacks by inhibiting leukocyte migration. ▪ Probenecid is a uricosuric agent that inhibits the tubular reabsorption of uric acid.

PHARMACOKINETICS[19,20]

Drug	Absorption (%)	Half-Life (hours)	Metabolism	Excretion (%)
allopurinol	90	1-2 oxypurinol 15 (range 12 to 30)	oxypurinol	Predominantly renal
colchicine (Colcrys)[21]	45	26.6-31.2	Three metabolites	Fecal and urinary excretion
febuxostat (Uloric)[22]	> 49	5-8	Four active metabolites	Renal: 49 Feces: 45
pegloticase (Krystexxa)[23]	100	nr	nr	nr
probenecid	Complete absorption	3-8 hrs; dose dependent	Active metabolites	Predominantly renal

Pharmacokinetic data are not available for colchicine/probenecid combination product.

CONTRAINDICATIONS/WARNINGS[24,25,26,27,28, 29]

allopurinol

Allopurinol is contraindicated in patients with a history of a severe reaction to allopurinol; do not rechallenge patients.

Hepatotoxicity: A few cases of reversible clinical hepatotoxicity have been noted in patients taking allopurinol, and in some patients, asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed.

Hypersensitivity Reactions: Allopurinol should be discontinued at the first appearance of a skin rash or other signs of an allergic reaction. In some cases, skin rash may be followed by a more severe hypersensitivity reaction such as exfoliative, urticarial, and purpuric lesions as well as Stevens-Johnson syndrome, and/or generalized vasculitis, irreversible hepatotoxicity, or death. Hypersensitivity reactions may be increased in patients with renal impairment and receiving thiazides. Use with caution and observe patients closely.

Drowsiness: Due to the occasional occurrence of drowsiness, patients should be alerted to use caution when engaging in activities where alertness is mandatory.

Allopurinol 300 to 600 mg daily should be reduced by one-third to one-fourth in patients receiving mercaptopurine and azathioprine. Use caution and monitor for toxic effects.

colchicine

Patients with renal or hepatic impairment should not be given colchicine in conjunction with efflux transporter P-glycoprotein (P-gp) or strong CYP3A4 inhibitors (examples: clarithromycin and cyclosporine). Life-threatening and fatal colchicine toxicity has been reported with colchicine taken in therapeutic doses in these patient populations.

Colchicine is a P-gp and CYP3A4 substrate and life-threatening and fatal drug interactions have been reported in patients treated with colchicine when given with P-gp or strong CYP3A4 inhibitors. If treatment with a P-gp or strong CYP3A4 inhibitor is required in patients with normal renal and hepatic function, the patient's dose of colchicine may need to be reduced or interrupted.

Fatal overdoses, both accidental and intentional, have been reported in adults and children who have ingested colchicine. Colchicine should be kept out of reach of children. Blood dyscrasias including myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, and aplastic anemia have been reported with therapeutic doses of colchicine.

Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk for neuromuscular toxicity. Concurrent use of atorvastatin, simvastatin, pravastatin, fluvastatin, gemfibrozil, fenofibrate, fenofibric acid, or benzafibrate (themselves associated with myotoxicity) or cyclosporine may potentiate myopathy development. Once colchicine is stopped, the symptoms generally resolve within one week to several months.

Elderly or debilitated patients should use colchicine with caution due to their susceptibility to cumulative toxicity.

Colchicine should be used cautiously in patients with preexisting bone marrow suppression. Prolonged administration of colchicine has been associated with bone marrow suppression including blood dyscrasias, such as agranulocytosis, thrombocytopenia, or aplastic anemia. Patients with dental disease should use colchicine with caution. If possible, dental work should be performed prior to initiating colchicine therapy or deferred until blood counts return to normal.

Colchicine should not be used as an analgesic medication.

Risk and Evaluation Mitigation Strategy (REMS) Program

The FDA requires that a patient medication guide be distributed with each colchicine (Colcrys) prescription.

febuxostat (Uloric)

Febuxostat (Uloric) is contraindicated in patients being treated with azathioprine or mercaptopurine.

Gout Flare: After initiation of febuxostat, an increase in gout flares is often observed. A reduction in serum uric acid levels occur which results in the mobilization of urate from tissue deposits and causes gout flares. In order to prevent gout flares when febuxostat is initiated, concurrent prophylactic treatment with an NSAID or colchicine is recommended for up to six months.

Cardiovascular Events: Compared to allopurinol, randomized controlled trials have shown that febuxostat has a higher rate of cardiovascular thromboembolic events [cardiovascular deaths, non-fatal myocardial infarctions (MI) and non-fatal strokes]. However, no causal relationship with febuxostat has been established. Prescribers should monitor for signs and symptoms of MI and stroke.

Liver Enzyme Elevation: Transaminase elevations greater than three times the upper limit of normal have been observed in febuxostat-treated patients. Assessment of liver function is recommended at two and four months following the start of febuxostat therapy and periodically thereafter. The transaminase elevations have not had any dose-effect relationship noted.

pegloticase (Krystexxa)

Patients with a G6PD deficiency should not use pegloticase because it increases the risk of hemolysis and methemoglobinemia. Patients who are at a higher risk for a G6PD deficiency (patients of Mediterranean or African ancestry) should be screened for G6PD deficiency before initiating pegloticase.

Pegloticase should be administered to patients in a health care setting in order to manage anaphylaxis. Anaphylaxis has been reported in 6.5 percent of the patients using pegloticase every two weeks compared to zero percent in placebo treated patients. Anaphylactic reactions can occur with any infusion and will usually present within the first two hours of the infusion. However, patients should be monitored after the infusion as delayed type hypersensitivity reactions have occurred. Patients should undergo pre-treatment with antihistamines and corticosteroids prior to using pegloticase. Anaphylaxis risk is higher in patients with uric acid levels above 6 mg per dL especially when two consecutive levels above 6 mg per dL exist. Patient's serum uric acid levels should be monitored prior to infusions and discontinuation of therapy may be warranted if levels increase above 6 mg per dL.

Infusion reactions have been reported in patients using pegloticase (26 to 41 percent) compared to placebo (five percent). The reactions occurred despite using the pre-treatment medications: oral antihistamines, intravenous corticosteroids, and/or acetaminophen. Pegloticase should be infused over at least 120 minutes and therapy should be slowed or stopped and restarted at a slower rate if infusion reactions occur. Infusion reaction risk is higher in patients with uric acid levels above 6 mg per dL especially when two consecutive levels above 6 mg per dL exist. Patient's serum uric acid levels should be monitored prior to infusions and discontinuation of therapy may be warranted if levels increase above 6 mg per dL.

Before starting pegloticase it is recommended that oral urate-lowering medications be discontinued and not restarted during pegloticase therapy. The combination of oral urate-lowering therapy and pegloticase may blunt the increase of serum uric acid levels.

Patients may experience an increase in gout flares when initiating pegloticase because of mobilization of urate from tissue deposits which alters serum uric acid levels. Unless contraindicated or an intolerance exists, non-steroidal anti-inflammatory drugs or colchicine are recommended starting at least one week before beginning pegloticase and for six months thereafter.

Pegloticase has not been studied in patients with congestive heart failure. However, caution should be exercised since some patients experienced exacerbations of congestive heart failure during clinical trials.

There are no controlled trials demonstrating the safety and efficacy of re-treatment with pegloticase after stopping therapy for greater than four weeks. Patients receiving re-treatment may be at a higher risk for anaphylaxis and infusion reactions due to the immunogenicity of pegloticase. Patients receiving re-treatment should be monitored closely.

probenecid and probenecid/colchicine

Probenecid is contraindicated in an acute attack of gouty arthritis. Probenecid should be initiated after the acute attack. Probenecid is also contraindicated in patients with blood dyscrasias, uric acid kidney stones, coadministration with salicylates, and hypersensitivity to probenecid. Children less than two years of age also should not receive probenecid.

Caution should be used with probenecid in patients with a known history of sulfonamide hypersensitivity as probenecid has a sulfonamide side chain. However, probenecid does not contain the N4 aromatic amine or the N1-substituent that is present in sulfonamide antibiotics and thought to be responsible for hypersensitivity-type adverse reactions.

Probenecid use to increase serum penicillin concentrations is not recommended for patients with renal impairment. Probenecid should not be given to patients with renal failure or renal disease associated with moderate to severe renal impairment (glomerular filtration rate < 50 mL/min). Probenecid is completely ineffective when the CrCl is < 30 mL/min.

Probenecid should be used with caution in patients with peptic ulcer disease because of a possible increase in gastrointestinal (GI) adverse reactions.

DRUG INTERACTIONS[30,31,32,33,34,35]

allopurinol

Allopurinol prolongs the half-life of the anticoagulant, dicumarol, therefore monitor prothrombin times and INR when allopurinol and oral anticoagulants are administered concurrently. Monitor cyclosporine levels and adjust cyclosporine dose appropriately if used concurrently with allopurinol due to a potential for an increase in cyclosporine levels.

By inhibiting xanthine oxidase, allopurinol inhibits the conversion of mercaptopurine, 6-MP, to its inactive metabolites.[36] As a result, the myelosuppressive effects and other side effects of 6-MP will be enhanced. Allopurinol should be avoided in patients receiving mercaptopurine. If this is not possible, the dose of 6-MP should be reduced. Allopurinol should not be administered with azathioprine as the risk of toxicity (bone marrow suppression, leucopenia, and pancytopenia) due to azathioprine may increase.[37]

Patients with renal impairment who receive allopurinol and thiazide diuretics are at an increased risk of hypersensitivity reactions.[38]

colchicine (Colcrys)

Colchicine is a substrate of the efflux transporter P-gp. The CYP3A4 enzyme is the main cytochrome P450 enzyme, of those tested, involved in the metabolism of colchicine. Increased concentrations of colchicine are likely if colchicine is administered with drugs that inhibit P-gp, most of which also inhibit CYP3A4. Fatal drug interactions have been reported.

For concurrent therapy with strong CYP450 3A4 inhibitors including atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin; colchicine requires a dose reduction due to the significantly higher colchicine levels. For gout flares, colchicine should be reduced to 0.6 mg for one dose then 0.3 mg given one hour later. Do not repeat colchicine gout flare treatment for at least three days. For the prophylaxis of gout flares patients should receive an adjusted dose of 0.3 mg once daily if the intended dose was 0.6 mg twice daily and 0.3 mg once every other day if the original intended dose was 0.6 mg once daily. For FMF, maximum daily dose of colchicine is 0.6 mg per day.

Higher colchicine levels have been observed in moderate CYP450 3A4 inhibitors; therefore, dose reduction of colchicine is recommended. For moderate CYP 450 3A4 inhibitors (amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil), colchicine should be

given at the usual dose for gout flares, but the treatment should not be repeated for at least three days. For the prophylaxis of gout flares an adjusted dose of 0.3 mg twice daily or 0.6 mg once daily should be used when the intended original dose was 0.6 mg twice daily and 0.3 mg once daily should be used when the intended dose was 0.6 mg once daily. For FMF, colchicine dose is reduced to 1.2 mg per day for adults.

Dose reduction is warranted as significantly higher colchicine plasma levels are expected with concurrent administration with a P-gp inhibitor. For P-gp inhibitors such as cyclosporine and ranolazine, colchicine for the treatment of gout flares is given as 0.6 mg for one dose. Do not repeat for at least three days. For the prophylaxis of gout flares the adjusted dose is 0.3 mg daily when the original dose was 0.6 mg twice daily and the adjusted dose is 0.3 mg once a day every other day when the original dose was 0.6 mg once daily. For FMF, colchicine dose is reduced to 0.6 mg per day.

Pharmacokinetics and/or pharmacodynamic interactions have been reported when atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, fibrates, or gemfibrozil are used concurrently with colchicine. The combinations have resulted in myopathy and rhabdomyolysis (including a fatality). Digoxin is a P-gp substrate; rhabdomyolysis has been reported with concurrent use of colchicine and digoxin. The potential benefits and risks of the combination therapy should be weighed. Patients should be monitored carefully for any signs or symptoms of muscle pain, tenderness, or weakness especially during early therapy. Monitoring creatine phosphokinase (CPK) will not necessarily prevent severe myopathy occurrence.

Treatment of gout flares is not recommended for patients receiving prophylactic therapy with colchicine and CYP 3A4 inhibitors.

febuxostat (Uloric)

Febuxostat has been shown to alter the metabolism of theophylline in humans based on a drug interaction study in healthy subjects. Caution should be used when administering the drugs together.

Drug interaction studies have not been conducted to examine febuxostat with other drugs that are metabolized by xanthine oxidase. Inhibition of xanthine oxidase by febuxostat may cause increased plasma concentrations of these drugs leading to toxicity.

pegloticase (Krystexxa)

No clinical studies have been conducted with pegloticase and other drugs to determine drug interactions. There may be potential for binding with other PEGylated products since anti-pegloticase antibodies appear to bind to the PEG portion of the drug.

probenecid

Probenecid inhibits the renal tubular secretion of many drugs including: acyclovir, valacyclovir, famciclovir, penicillins, sulbactam, tazobactam, gatifloxacin, nitrofurantoin, zidovudine, zalcitabine, dapsone, pantothenic acid, rifampin, sulfonamides, sulfonylureas, captopril, methotrexate, ciprofloxacin, clofibrate, ganciclovir, imipenem/cilastatin, and most cephalosporins. Higher systemic exposure and longer half-life may occur which could lead to toxic levels of these agents.

Probenecid and methotrexate used concurrently is not recommended because the combination can increase the risk of uric acid neuropathy. Probenecid inhibits the tubular secretion of nalidixic acid

which may result in decreased efficacy for treatment of urinary track infections and increased risk of systemic adverse effects.

Probenecid has been shown to decrease the tubular secretion of cidofovir and may minimize cidofovir-induced nephrotoxicity. While concomitant administration of probenecid is recommended during cidofovir therapy, clinicians should note that cidofovir serum concentrations also increase. Clinicians should be alert to increased cidofovir adverse reactions, particularly in patients with compromised renal function.

Probenecid and salicylates used concurrently is contraindicated. The uricosuric actions of probenecid are inhibited by salicylates even though the plasma concentration of salicylates is not influenced by probenecid.

Probenecid can decrease the renal clearance of NSAIDs, especially indomethacin, ketoprofen, ketorolac, and naproxen, increasing the possibility of adverse effects.

Natriuresis and plasma renin activity increases caused by diuretics such as bumetanide, furosemide, and indapamide can be interfered with due to probenecid. The effects of probenecid can be antagonized by these diuretics as they can increase the levels of serum uric acid.

The anticoagulant effects of heparin may be increased by concomitant administration of probenecid.

ADVERSE EFFECTS[39,40]

Drug	Arthralgia	Rash	Diarrhea	Nausea	LFT Elevations
allopurinol[41]	<1	1-3	>1	>1	>1
colchicine (Colcrys)[42]	nr	Reported	23-77	4-17	Reported
febuxostat (Uloric)[43] allopurinol placebo	0.7-1.1 0.7 (0)	0.5-1.6 1.6 (0.7)	nr	1.1-1.3 0.8 (0.7)	4.6-6.6 4.2 (0.7)
pegloticase (Krystexxa)[44]	nr	nr	nr	12	nr
probenecid	nr	Reported	Reported	Reported	nr
probenecid – colchicine	nr	Reported	Reported	Reported	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

The most common adverse events associated with pegloticase use include: immunogenicity (92 percent); gout flares (77 percent); infusion reactions (26 percent); contusion or ecchymosis (11 percent); nasopharyngitis (seven percent); anaphylactic reaction (6.5 percent); constipation (six percent); chest pain (six percent); and vomiting (five percent). Congestive heart failure has been reported in two patients using pegloticase during clinical trials and four patients had exacerbations of pre-existing congestive heart failure.

SPECIAL POPULATIONS[45,46,47,48,49,50]

Pediatrics

Safety and effectiveness of allopurinol, febuxostat (Uloric), and pegloticase (Krystexxa), in pediatric patients have not been established. Probenecid is contraindicated in children less than two years of age. Colchicine (Colcrys) is indicated in the management of FMF for children ages four years and older.

For the treatment and prevention of gout flares, safety and effectiveness of colchicine have not been established in pediatric patients.

Pregnancy

All products in this review, except for probenecid, are Pregnancy Category C. Probenecid is Pregnancy Category B.

Renal Insufficiency: No dose adjustment for febuxostat (UIoric) is necessary in patients with mild or moderate renal impairment (creatinine clearance [CrCl] 30-89 mL/min). Caution should be taken in patients with severe renal impairment (CrCl <30 mL/min) as there is no sufficient data in this patient population. The use of febuxostat has not been studied in patients with end stage renal disease who are also on dialysis. Probenecid should not be used in patients with estimated CrCl of less than 50 mL/min.

Allopurinol requires dose adjustment in renal insufficiency. For patients with a CrCl of 10 to 20 mL/min, a daily dose of 200 mg is recommended and for patients with a CrCl less than 10 mL/min, a daily dose of 100 mg is recommended. In patients with extreme renal impairment (CrCl <3 mL/min), the interval between doses may need to be lengthened.

In the presence of renal impairment (CrCl <30 mL/minute), colchicine (Colcrys) dosing for treatment of gout flares should be repeated no more than once every two weeks, whereas dosing for FMF should be continued but adjusted based upon the patients estimated creatinine clearance. For patients undergoing dialysis, the total recommended colchicine (Colcrys) dose for the treatment of gout flares should be reduced to 0.6 mg for one dose, whereas for FMF patients, the starting dose should be 0.3 mg per day. No dosage adjustment is necessary for colchicine for patients with CrCl > 30 mL/minute; however, monitoring for adverse effects should be performed. Patients with severe renal impairment should receive colchicine 0.3 mg daily for the prevention of gout flares. For patients undergoing dialysis and receiving colchicine for the prevention of gout flares, the starting dose of colchicine should be 0.3 mg given twice weekly with close monitoring. Treatment of gout flares with colchicine is not recommended in patients with renal impairment who are receiving colchicine for prophylaxis.

For patients with FMF and renal insufficiency, dosage of colchicine should be reduced for patients with CrCl < 30 mL/minute to 0.3 mg daily with a dose increase carefully monitored for adverse effects. For patients undergoing hemodialysis, the total recommended starting dose of colchicine should be 0.3 mg daily.

Hepatic Insufficiency: No dose adjustment for febuxostat (Uloric) is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). Caution should be taken in patients with severe hepatic impairment (Child-Pugh Class C) as there is no sufficient data in this patient population. No dose adjustment for allopurinol is necessary in patients with hepatic impairment.

For treatment or prevention of gout flares in patients with mild to moderate hepatic impairment, no dose adjustment for colchicine (Colcrys) is required. However, in patients with severe hepatic impairment, the colchicine (Colcrys) dose does not need to be adjusted but should be considered. A treatment course should be repeated no more than once every two weeks. Treatment of gout flares with colchicine is not recommended in patients with hepatic impairment who are receiving colchicine for prophylaxis. Colchicine dose adjustment is not required for prophylaxis of gout flares in patients with mild to moderate hepatic impairment but patients should be closely monitored. However, dose reductions should be considered in patients with severe hepatic impairment. Monitoring should be

performed in patients with FMF and mild to moderate hepatic impairment and dose reductions should be considered in patients with severe hepatic impairment.

DOSAGES[51,52]

Drug	Initial Dose	Titration	Dose Adjustments	Availability
allopurinol[53]	100 mg daily	To reduce the possibility of flare-up of acute gouty attacks start at 100 mg daily, increased by 100 mg weekly until serum urate ≤ 6 mg/dL. Maximum daily dose is 800 mg. Mild cases of gout: 200—300 mg per day Moderate to severe trophaceous gout: 400—600 mg per day	CrCl 10-20 mL/min: 200 mg daily CrCl 3-9 mL/min: 100 mg/day	100, 300 mg tablets
febuxostat (Uloric)[54]	40 mg daily	If serum uric acid > 6 mg/dL after two weeks, increase to 80 mg daily.	Can be taken without regard to food or antacid use	40, 80 mg tablets
pegloticase (Krystexxa)[55]	8 mg administered as an intravenous infusion every two weeks			8 mg/mL in a 2 mL single use vial. Store in refrigerator. Do not freeze or shake. Protect from light.
probenecid	250 mg twice daily for 1 week, then 500 mg twice daily	Dose may be increased by 500 mg increments per day every 4 weeks. Maximum dose is 2 gm per day.	Administer with food or antacids to minimize GI adverse effects.	500 mg tablet
probenecid – colchicine	1 tablet daily for 1 week, then 1 tablet twice daily	If tolerated and if symptoms are not controlled or the 24-hour uric acid excretion is not > 700 mg, increase by 1 tablet/day every 4 weeks; Continue for 6 months once serum uric acid concentrations are within normal limits; thereafter, dose may be decreased by 1 tablet/day every 6 months.	Do not initiate combination therapy until an acute gout attack has been resolved. If a patient is controlled on therapy and an acute attack occurs, the maintenance dosage may be continued.	0.5 mg/500 mg tablet

Other dosages

Probenecid used as an adjuvant to antibiotic therapy:

- **Adults (>14 years):** 2 gm daily in divided doses
- **Children (2-14 years and > 50 kg):** 2 gm daily in divided doses

- **Children (2-14 years and ≤ 50 kg):** 25mg/kg as a single dose then 40 mg/kg/day in four divided doses. Maximum 2 gm daily.

Probenecid used in combination with penicillin or ampicillin for treatment of Gonorrhea:

- **Adults:** 1 gm single dose

Pegloticase should be administered in a health care setting intravenously over at least 120 minutes by gravity feed, syringe-type pump, or infusion pump. Pegloticase should not be administered as an intravenous push or bolus. In order to minimize the risk of anaphylaxis and infusion reactions patients should be treated with pre-infusion medications (e.g. antihistamines, corticosteroids).

Dosages (continued)

Drug	Initial Dose	Titration	Dose Adjustments	Availability
colchicine (Colcrys)[56]	Gout Flare Treatment: 1.2 mg at the first sign of a flare then 0.6 mg one hour later.	--	Gout Flare Treatment: Renal (CrCl<30 mL/min) or Severe Hepatic Insufficiency: do not repeat treatment for 2 weeks. Hemodialysis: 0.6 mg once and do not repeat for 2 weeks. Drug Interactions see table	0.6 mg tablet Administer orally without regard to meals.
	Gout Flare Prevention: 0.6 mg once or twice daily in adults and adolescents (>16 years). Maximum daily dosage is 1.2 mg.		Gout Flare Prevention: Renal (CrCl<30mL/min): 0.3 mg daily. Hemodialysis: 0.3 mg twice weekly with close monitoring. Drug Interactions see table	
	FMF: adults and children >12 years:1.2-2.4 mg per day ages 6-12 years: 0.9-1.8 mg per day ages 4-6 years: 0.3-1.8 mg per day.	FMF: Give total daily dose in one or two divided doses. Increase or decrease the dose as indicated and as tolerated in increments of 0.3 mg/day, not to exceed the maximum recommended daily dose.	FMF: Renal Insufficiency If CrCl<30 mL/min including dialysis: 0.3 mg daily and monitor for adverse effects when increasing dose. Severe Hepatic Impairment: consider dose reduction and monitor for adverse effects. Drug Interactions see table.	

Dosages (continued)

colchicine (Colcrys) drug interactions and dosage adjustments[57]

If patients are taking or have recently completed treatment with drugs listed in the table below within the prior 14 days, the dose of colchicine (Colcrys) should be reduced as listed below.

Drug Interactions with colchicine	Recommended dose for Gout Flares	Recommended dose for management of FMF
Strong CYP 3A4 Inhibitors: atazanavir, clarithromycin, darunavir/ritonavir, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, tipranavir/ritonavir	Treatment of Gout Flares: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days. Prevention of Gout Flares: 0.3 mg daily or every other day	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
Moderate CYP 3A4 Inhibitors: amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil	Treatment of Gout Flares: 1.2 mg (2 tablets) x 1 dose. Dose to be repeated no earlier than 3 days. Prevention of Gout Flares: 0.3 mg twice daily or 0.6 mg once daily or 0.3 mg once daily	Maximum daily dose of 1.2 mg (may be given as 0.6 mg twice a day)
P-gp Inhibitors: cyclosporine, ranolazine	Treatment of Gout Flares: 0.6 mg (1 tablet) x 1 dose. Dose to be repeated no earlier than 3 days. Prevention of Gout Flares: 0.3 mg daily or every other day	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)

Treatment of gout flares is not recommended for patients receiving prophylactic therapy with colchicine and CYP 3A4 inhibitors.

CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Current literature is lacking in the evaluation of colchicine and probenecid as the combination.

febuxostat (Uloric) and allopurinol

In a 52-week randomized, double blind trial in patients (n=762) with serum urate concentrations of at least 8 mg/dL, patients were randomly assigned to receive either febuxostat 80 or 120 mg or allopurinol 300 mg per day (FACT).[58] Prophylaxis against gout flares with naproxen or colchicine was provided during weeks 1 through 8. The primary end point, a serum urate concentration of less than 6.0 mg per deciliter at the last three monthly measurements, was reached in 53 percent of patients receiving febuxostat 80 mg, 62 percent of patients on febuxostat 120 mg, and 21 percent of those receiving allopurinol (p<0.001 for the comparison of each febuxostat group with the allopurinol group). Although the incidence of gout flares diminished with continued treatment, the overall incidence during weeks 9 through 52 was similar in all groups: 64 percent of patients receiving 80 mg of febuxostat, 70 percent of those receiving 120 mg of febuxostat, and 64 percent of those receiving allopurinol (p=0.99 for 80 mg of febuxostat versus allopurinol; p=0.23 for 120 mg of febuxostat versus allopurinol). More patients in the high-dose febuxostat group than in the allopurinol group (p=0.003) or the low-dose febuxostat group discontinued the study. Four of the 507 patients in the two febuxostat groups (0.8 percent) and none of the 253 patients in the allopurinol group died; all deaths were from causes that the investigators (while still blinded to treatment) judged to be unrelated to the study drugs (p=0.31 for the comparison between the combined febuxostat groups and the allopurinol group). The study compared moderate dose of allopurinol to high dose febuxostat.

Febuxostat 80, 120 or 240 mg once daily showed significantly greater urate-lowering efficacy than allopurinol 100 mg (adjusted for renal impairment) or 300 mg once daily in a 28-week, randomized, double-blind, placebo-controlled trial (APEX) in patients (n=1,072) with gout and hyperuricemia.[59] Patients had gout with normal to impaired renal function (serum creatinine level >1.5 to ≤2.0 mg/dL). The primary endpoint, achievement of serum urate levels < 6 mg/dL for last three months, occurred more frequently with febuxostat [80 mg (48 percent), 120 mg (65 percent), and 240 mg (69 percent) all p-values ≤0.05] than with allopurinol (22 percent) or placebo (zero percent). A significantly (p<0.05) higher percentage of subjects with impaired renal function treated with febuxostat 80 mg (4 [44 percent] of 9), 120 mg (5 [45 percent] of 11), and 240 mg (3 [60 percent] of 5) achieved the primary end point compared with those treated with 100 mg of allopurinol (0 [zero percent] of 10). Adverse events were similar across groups, although diarrhea and dizziness were more frequent in the febuxostat 240 mg group. The primary reasons for withdrawal were similar across groups except for gout flares, which were more frequent with febuxostat than with allopurinol. The study compared moderate dose of allopurinol to high dose febuxostat.

In a Phase 3, randomized, double-blind study, febuxostat 40 and 80 mg daily and allopurinol 300 mg daily (200 mg daily for renal impairment) were compared for safety and efficacy over six months in 2,226 patients with gout.[60] Prophylaxis for gout flares was colchicine 0.6 mg daily or naproxen 250 mg twice daily plus lansoprazole 15 mg daily. Prophylaxis for gout flares with naproxen was not administered to patients with CrCl < 50 mL/minute. Primary outcome parameters were the proportion of all subjects with serum uric acid levels < 6 mg/dL and the proportion of subjects with mild (CrCl 60 to 89 mL/minute) to moderate (30 to 59 mL/minute) renal impairment with serum uric acid levels < 6 mg/dL. Sixty-five percent of patients had renal impairment. A total of 418 subjects prematurely discontinued treatment, 120 within the first month of treatment. The proportions of patients achieving serum uric acid <6 mg/dL were 45.2 percent of febuxostat 40 mg group, 67.1 percent of febuxostat 80 mg group, and 42.1 percent of allopurinol group. Urate lowering efficacy of febuxostat 40 mg was non-inferior to allopurinol; the difference in the response rates between the two groups was not significant.

The urate lowering response rate with febuxostat 80 mg compared with either febuxostat 40 mg (21.9 percent) or allopurinol (24.9 percent) was significant (p<0.001). The urate lowering response rate in the febuxostat 80 mg group (72 percent) with renal impairment was greater than that observed in the febuxostat 40 mg (49.7 percent) and allopurinol groups (42.3 percent; p≤0.001 for each comparison). For patients with renal impairment, the urate lowering response rate was greater for febuxostat 40 mg than allopurinol (p=0.021). Adverse events and discontinuation rates were similar among the groups.

colchicine plus allopurinol

A double-blind, placebo-controlled trial evaluated the use of colchicine to prevent acute gout flares during initiation of allopurinol in 43 patients with chronic gouty arthritis.[61] Patients starting allopurinol for crystal-proven chronic gouty arthritis were randomized to colchicine 0.6 mg twice daily (n=21) or placebo (n=22). Allopurinol was initiated at 100 mg daily and titrated in 100 mg increments at two to three week intervals to achieve serum uric acid levels < 6.5 mg/dL. For patients with renal impairment (creatinine clearance 20-50 mL/min), allopurinol dose was escalated in 50 mg increments. All patients achieved serum uric acid < 6.5 mg/dL. Patients were followed for acute gout flares for three months after attainment of serum uric acid concentrations < 6.5 mg/dL. Patients treated with colchicine experienced fewer total flares (0.52 versus 2.91, p=0.008), fewer flares from zero to three months (0.57 versus 1.91, p=0.022), fewer flares from three to six months (0 versus 1.05, p=0.033), less severe flares as reported on visual analog scale (3.64 versus 5.08, p=0.018), and fewer recurrent gout flares (p=0.001). Colchicine was well tolerated. Administration frequency of colchicine was reduced from twice daily to once daily in 62 percent of patients compared to placebo (36 percent, p=0.094). Discontinuation rates were similar. Colchicine prophylaxis during initiation of allopurinol for chronic gouty arthritis reduces the frequency and severity of acute flares, and reduces the likelihood of recurrent flares.

colchicine (Colcrys)

The efficacy of a low dosage regimen of oral colchicine (1.2 mg followed by 0.6 mg one hour later) for treatment of gout flares was assessed in a multicenter, randomized, double-blind, placebo-controlled, parallel group, one week, dose comparison study.[62,63] Patients meeting American College of Rheumatology (ACR) criteria for gout were randomly assigned to three groups: high-dose colchicine (n=52) (1.2 mg, then 0.6 mg hourly × six hours [4.8 mg total]); low-dose colchicine (n=74) (1.2 mg, then 0.6 mg in one hour [1.8 mg total] followed by 5 placebo doses hourly); or placebo (n=58) (2 capsules, then 1 capsule hourly × six hours). Patients took the first dose within 12 hours of the onset of the flare and recorded pain intensity and adverse events over 72 hours. The efficacy of colchicine was measured based on response to treatment in the target joint, using patient self assessment of pain at 24 hours following the time of first dose as recorded in the diary. A responder was one who achieved at least a 50 percent reduction in pain score at the 24-hour post-dose assessment relative to the pre-treatment score and did not use rescue medication prior to the actual time of 24-hour post-dose assessment. Rates of response were similar for the recommended low-dose treatment group (37.8 percent; p=0.005 versus placebo) and the non-recommended high-dose group (32.7 percent; p=0.034 versus placebo) but were higher as compared to the placebo group (15.5 percent). Rescue medication within the first 24 hours was taken by 31.1 percent in the low-dose group (p=0.027 versus placebo), 34.6 percent in the high-dose group (p=0.103 versus placebo), and 50 percent in the placebo group. Adverse event profile was similar in the low-dose group and placebo. Patients in the high-dose colchicine group reported significantly more diarrhea, vomiting, and other adverse events compared with the low-dose

and placebo groups. Diarrhea was reported in 76.9 percent of patients in the high-dose group with 19.2 percent reporting severe diarrhea (odds ratio 21.3, 95% CI, 7.9 to 56.9). In the low dose group, 23 percent of patients reported diarrhea (odds ratio 1.9, 95% CI, 0.8 to 4.8) with no reports of severe diarrhea. The manufacturer of Colcrys funded the study.

The evidence for the efficacy of colchicine in patients with FMF is derived from three randomized, placebo-controlled studies with a total of 48 adult patients.[64] Patients who were compliant had a reduced rate of attacks compared to placebo. However, data are incomplete for one of the studies. Noncompliance was reported in about one-third of patients. Open-label experience with colchicine in adults and children with FMF is consistent with the randomized, controlled trial experience and was utilized to support information on the safety profile of colchicine and for dosing recommendations.

pegloticase (Krystexxa)

Two replicate, double-blinded, randomized, placebo controlled trials were conducted for six months in 225 patients throughout 56 rheumatology clinics in the United States, Mexico, and Canada for the purposes of assessing the efficacy and tolerability of pegloticase in the management of refractory chronic gout.[65] Patients were 18 years or older and had severe gout, allopurinol intolerance or refractoriness, serum uric acid concentrations of 8 mg per dL or more, and at least one of the following conditions: three or more self-reported gout flares within the last 18 months, at least one tophi, and gouty arthropathy. Patients who were receiving urate-lowering medications at the onset of screening were required to undergo a one week washout. Prophylactic gout therapy was started one week before the pegloticase infusion and continued throughout the study. Patients also received pre-treatment with medications to protect against infusion reactions. Patients were randomized into three study groups in a 2:2:1 ratio: pegloticase biweekly, pegloticase monthly, or placebo, respectively. In the pooled analysis, the portion of uric acid (UA) responders (defined as plasma UA less then 6 mg per dL for greater than or equal to 80 percent of the time during months three and six) in the pegloticase groups were significantly greater than placebo ($p < 0.001$). When examining response rates by dose, the pegloticase biweekly group had response rates of 47 percent (20/43; 95% CI) and 38 percent (16/42; 95% CI) in the two trials. Patients treated with monthly pegloticase had a response rate of 20 percent (8/41; 95% CI) and 49 percent (21/43; 95% CI). The response rates in the placebo groups were zero percent (95% CI). The study also found that non-responder patients had UA levels below 6 mg per dL through week ten but then remained above the target level thereafter suggesting an emergence of decreased urate-lowering efficacy early in treatment. The study also found that 41 percent of the biweekly pegloticase, 21 percent of the monthly pegloticase, and seven percent of the placebo patients experienced a complete response to at least one tophi ($p=0.002$ and $p=0.2$, respectively). Immunogenicity occurred in 134 of the 150 patients treated with pegloticase indicated by the presence of pegloticase antibodies (95% CI). Overall the study concluded that pegloticase provided significant improvements in patient quality of life, physical function, and pain levels due to its ability to reduce uric acid levels compared to placebo.

META-ANALYSIS

A systematic review evaluated the efficacy and safety of colchicine for the relief of the signs and symptoms of acute gout. Randomized controlled clinical trials were gathered from numerous databases. One randomized controlled trial with 43 patients compared colchicine to placebo for the acute treatment of gout was identified. The results favored the use of colchicine over placebo with an

absolute reduction of 34 percent for pain and 30 percent reduction in clinical symptoms such as tenderness on palpation, swelling, redness, and pain. The number-needed-to-treat with colchicine versus placebo to reduce pain was three and the number-needed-to-treat to reduce clinical symptoms was two. All patients experienced gastrointestinal adverse effects, namely diarrhea and/or vomiting. No studies comparing colchicine to NSAIDs or corticosteroids were identified. Due to the high likelihood of adverse effects, the systematic review concluded that colchicine should be used as second line therapy when NSAIDs or corticosteroids are contraindicated or ineffective.

SUMMARY

Acute gouty arthritis can be treated with colchicine, NSAIDs, and intra-articular corticosteroid injections. After an initial gout attack, the choice of urate-lowering medications is probenecid, colchicine/probenecid combination, or xanthine oxidase inhibitors. Probenecid promotes uric acid excretion by inhibiting the tubular reabsorption of filtered and secreted urate thereby increasing urate excretion. Xanthine oxidase inhibitors, allopurinol, and febuxostat, inhibit uric acid production. Febuxostat (Uloric) reduced serum urate levels below 6 mg/dL in a significantly greater proportion of patients with gout and hyperuricemia compared to allopurinol; however the incidence of gout flares, a clinical outcome, does not appear lower with febuxostat compared to allopurinol.

Colchicine (Colcrys) is the first FDA-approved colchicine product. Colchicine has significant drug interactions and frequent gastrointestinal adverse effects; however, Colcrys is approved at a lower dosage for the treatment and prevention of gout flares than previously described. Colcrys is approved as an orphan drug for the treatment of FMF.

Pegloticase (Krystexxa) provides an effective alternative therapy to conventional oral urate-lowering medications for those patients who cannot take oral urate-lowering medications.

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